
Effects of blood pressure lowering treatment in acute stroke

Secondary analyses of the Scandinavian Candesartan Acute Stroke Trial

Thesis for the degree philosophiae doctor

by

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Oslo, March 2015

A handwritten signature in blue ink, appearing to read 'Astrid Gjerdrum Hornslien', with a stylized, cursive script.

Astrid Gjerdrum Hornslien

PREFACE

Every year, near 17 million people worldwide suffer a stroke and 6 million people die of stroke. The global burden is increasing and stroke is now the second leading cause of death and the fourth leading cause of global disease worldwide. In high-income countries, the incidence of stroke is decreasing, even though the actual number of stroke is increasing because of the ageing population. In low-income and middle-income countries, however, the incidence of stroke is increasing. The predictions for the next two decades suggest a tripling in stroke mortality in Latin America, the Middle East and sub-Saharan Africa (1).

Stroke refers to any damage to the brain or the spinal cord caused by an abnormality of the blood supply and is a clinical syndrome rather than a single disease. The World Health Organization (WHO) defines stroke as rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin (2). Advances in basic science, neuropathology and neuroimaging have improved the understanding of ischaemia, infarction and haemorrhage in the central nervous system and the American Heart Association and American Stroke Association (AHA/ASA) has proposed an updated definition of stroke, based on neurologic dysfunction caused by ischaemia with (*ischaemic stroke*) or without (*transient ischaemic attack*) acute infarction, or caused by a focal collection of blood (*haemorrhagic stroke*) (3).

Apoplexy was the first common term for stroke and comes from the Greek word *apoplexia*, which means ‘struck suddenly with violence’. The word *stroke* refers to being suddenly stricken. Hippocrates (around 400 BC) was probably the first to describe the sudden paralysis

often associated with ischaemic stroke and he also observed that there were many blood vessels connected to the brain. In the 17th century, Johann Jakob Wepfer described obstruction of the carotid and vertebral arteries as cause of apoplexy and furthermore, he was the first to demonstrate that apoplexy also was caused by an intracranial haemorrhage. In the same century, Thomas Willis described an almost asymptomatic carotid occlusion, prevented by the collateral circulation in the head and neck. Furthermore, he recognised transient ischaemic attacks and the phenomenology of embolism (4). In the 19th century, Rudolf Virchow described the mechanism of thromboembolism as a major risk factor of ischaemic stroke and 100 years later, Charles Miller Fischer did much to awaken clinical interest in stroke. During the last 25 years, there has been an explosive growth of interest in and knowledge about stroke. Epidemiologic studies identify more accurately the risk factors for stroke-prevention strategies, new surgical and medical treatments are possible and clinical trials evaluate the efficacy and safety of these treatments. Sophisticated neuroimaging and endovascular therapy have moved the management of acute stroke from passive-supportive to active, well-coordinated, multidisciplinary care (based on *Caplan's stroke: a clinical approach* (5)).

Leaders in science, medicine and politics have had their productivity cut by stroke, while some did not let this prevent them from ruling the world. Churchill, Roosevelt and Stalin had all suffered from stroke when meeting at the Yalta conference after the Second World War. History might have been different if these world leaders had not been affected by stroke (6).

Picture 1: Winston Churchill, Franklin Delano Roosevelt, and Joseph Stalin at the Yalta conference after the Second World War. All had severe cerebrovascular disease at the time. Photograph: Army Signal Corps, 1945.



In this thesis I have studied the effects of blood pressure lowering treatment in the acute phase of stroke on a number of effect variables, both after medium-term and long-term follow-up. The thesis is based on secondary analyses of the Scandinavian Candesartan Acute Stroke Trial.

LIST OF PAPERS

**I: Effects of candesartan in acute stroke on cognitive function and quality of life.
Results from the Scandinavian Candesartan Acute Stroke Trial**

Astrid G. Hornslien, Else C. Sandset, Philip M. Bath, Torgeir B. Wyller, and Eivind Berge, on Behalf of the Scandinavian Candesartan Acute Stroke Trial Study Group

Stroke 2013 Jul;44(7):2022-4.

**II: Effects of candesartan in acute stroke on activities of daily living and level of care
at 6 months**

Astrid G. Hornslien, Else C. Sandset, Torgeir B. Wyller, and Eivind Berge, on behalf of the Scandinavian Candesartan Acute Stroke Trial Study Group.

Journal of Hypertension 2015 (accepted)

**III: Effects of candesartan in acute stroke on vascular events during long-term
follow-up: Results from the Scandinavian Candesartan Acute Stroke Trial
(SCAST)**

Astrid G. Hornslien, Else C. Sandset, Jannicke Igland, Andreas Terént, Gudrun Boysen, Philip M. W. Bath, Gordon D. Murray, and Eivind Berge.

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ABBREVIATIONS

| | |
|----------|--|
| ACCESS | Acute Candesartan Cilxetil Therapy in Stroke Survivors |
| CVDNOR | The Cardiovascular Disease in Norway-project |
| ENOS | Efficacy of Nitric Oxide in Stroke |
| EQ-VAS | EuroQoL Visual Analogue Scale |
| ICD-10 | International Classification of Diseases version 10 |
| INTERACT | Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial |
| MMSE | Mini Mental State Examination |
| SCAST | Scandinavian Candesartan Acute Stroke Trial |
| WHO | The World Health Organisation |
| WHO-ICF | The World Health Organisation's International Classification of Functioning, Disability and Health |

INTRODUCTION

Hypertension is the predominant modifiable risk factor for stroke (7) and treatment of hypertension is well-established for both primary and secondary prevention (8). Extensive advances in stroke therapy have been achieved during the past years, but blood pressure management in acute stroke still remains controversial, due to lack of evidence from clinical trials and conflicting data from epidemiological and pathophysiological studies (9-12).

HIGH BLOOD PRESSURE IN ACUTE STROKE

High blood pressure is defined by the WHO as a systolic blood pressure ≥ 140 mmHg and/or a diastolic blood pressure ≥ 90 mmHg (13). Observational studies suggest that up to 75% of patients with acute stroke have high blood pressure at the time of hospital admission (14;15), with a spontaneous fall for most of the patients within 10-14 days (16). There is no single explanation for the initial high blood pressure and the contributing factors may vary in different subtypes of stroke. In a portion of these patients, the underlying cause is often an undiagnosed or inadequately treated hypertension that has been unmasked (17;18). In other patients, it may relate to the Cushing's reflex in cases in which the intracranial pressure is elevated or a rightward shift of the cerebral auto-regulatory curve in patients with a history of chronic hypertension (19). Lastly, a neuroendocrine response with activation of the sympathetic nervous system and the renin-angiotensin axis is also associated with an initial increase in the systemic blood pressure (20).

The initial rise of blood pressure in the acute phase can be a protective mechanism, preventing irreversible infarction of the ischaemic penumbra. On the other hand, raised blood pressure might increase cerebral oedema or haemorrhagic transformation in ischaemic stroke, or lead to haematoma expansion and rebleeding in haemorrhagic stroke (21). Most studies have shown that elevated blood pressure is associated with poor outcome (22;23) and a U-shaped relationship such that both low and high blood pressure is associated independently with increased early death and later death or dependency, is described for both ischaemic and haemorrhagic stroke patients in several populations (21;24).

BLOOD PRESSURE LOWERING IN ACUTE STROKE

Clinical practice has generally been to accept high blood pressure in the acute phase, based on a well-founded theory of the impaired cerebral auto-regulation in acute stroke (25). In this situation, cerebral perfusion becomes dependent on systemic blood pressure and rapid blood pressure lowering might decrease cerebral tissue perfusion and leads to further ischaemic damage, as suggested by a small trial of intravenous nimodipine (26). As previously mentioned, patients with chronic hypertension before stroke appear to have their auto-regulation shifted to a higher level, making the injured brain even more vulnerable to blood pressure lowering (27). However, clinical guidelines have recommended blood pressure reduction in the acute phase for patients with ischaemic stroke and blood pressure > 220/120 mmHg or end organ involvement and blood pressure > 200/100 mmHg. Blood pressure reduction is also recommended among patients with primary haemorrhagic stroke and systolic blood pressure > 200/120 mmHg and for patients eligible for thrombolytic therapy and systolic blood pressure > 185 mmHg and diastolic blood pressure > 110 mmHg (28-30).

Previous studies about the effect of blood pressure lowering in acute stroke have given conflicting results. Similar for them all was a small study sample and hence, neither study was powered to detect significant differences in clinical outcome.

The Cochrane Collaboration published in 2010 a review on vasoactive drugs for acute stroke, including 43 trials and 7,649 patients. The trials involved 16 combinations of drug classes and routes of administration, patients were recruited into trials within 6 to 168 hours and treatment duration varied from 24 hours to 9 months. Beta receptor antagonists, calcium channel blockers, glyceryl trinitrate, prostacyclin and mixed antihypertensive therapy each lowered blood pressure significantly during the first 3 days of treatment, but none of the drug classes significantly altered outcome (31).

Several trials found no benefit or even a detrimental effect of early blood pressure lowering in acute ischaemic stroke. The Intravenous Nimodipine West European Stroke Trial (INWEST) was a double-blind and placebo-controlled trial of intravenous nimodipine in patients with acute ischaemic stroke. The study was terminated after inclusion of 295 of the planned 600 patients because of indications of neurological worsening after intravenous infusion of nimodipine (26).

Other trials suggested that blood pressure lowering in acute ischaemic stroke was safe, including the Acute Candesartan Cilexetil Therapy in Stroke Survivors (ACCESS) study. The trial was a double-blind and placebo-controlled phase II trial of candesartan in patients with ischaemic stroke and elevated blood pressure. The trial aimed to recruit 500 patients, but was stopped prematurely after randomisation of 342 patients based on the results of an interim analysis. Patients treated with candesartan one week immediately following stroke had significantly lower risk of the composite endpoint of death and non-fatal vascular events when compared with placebo (32).

Furthermore, a pilot study of hyperacute blood pressure lowering in haemorrhagic stroke showed promising results. The Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT) reported that early intensive blood pressure lowering could reduce haematoma growth. In this trial, 404 hypertensive patients with primary intracranial haemorrhage diagnosed within 6 hours of symptom onset were randomised to intensive blood pressure lowering (target systolic blood pressure < 140 mmHg) or standard treatment of blood pressure (target systolic blood pressure < 180 mmHg) (33).

Larger trials were required, and the Scandinavian Candesartan Acute Stroke Trial (SCAST) was the first large trial to test whether benefits can be obtained from blood pressure lowering treatment in the acute phase. 2,029 hypertensive patients presenting within 30 hours of acute ischaemic or haemorrhagic stroke were randomised to the angiotensin receptor blocker candesartan or placebo. However, the trial could not show beneficial effects of treatment on the primary effect variables vascular events and functional outcome at 6 months (34).

EFFECT VARIABLES IN CLINICAL STROKE TRIALS

The classical clinical trial is designed to test efficacy of an intervention over a comparator, for example placebo or usual care. ‘Hard’ clinical endpoints, such as death or recurrent stroke, are useful, but do not fully capture the potential devastating effect of a non-fatal, disabling stroke. As stroke represents the second leading global cause of disability, an important consideration for any study of stroke interventions should be measures at the level of activities. Moreover, depression, cognitive impairment and communication deficits alone or in combination affect more than 25 % of stroke patients and affect their health-related quality of life (35;36). So far, no single measure fully describes all dimensions of stroke recovery and as an example, a

systematic review of 51 acute stroke drug interventions studies showed that 14 different measures of impairment, 11 different measures of activity limitation, one quality of life-measure and eight other miscellaneous measures were used (37). Each scale is unique and understanding the differences is important for the appropriate use in clinical practice and the interpretation of results reported in clinical trials.

The WHO has developed the International Classification of Functioning, Disability and Health (WHO-ICF), a comprehensive model of functioning and disability (38). It is a framework of health and health-related domains and aids classification of outcomes and helps decide on the appropriate measure for a particular purpose (Table 1).

Table 1: World Health Organisation's International Classification of Functioning, Disability, and Health. Modified from Duncan et al.(37)

| Illness of person | Synonym | Level of description | Outcome scales used in SCAST |
|----------------------------------|---|---------------------------------------|--|
| Pathology | Disorder/disease (e.g. ischaemic stroke) | Organ/organ system | Clinical endpoints |
| Impairment | Symptom/sign (e.g. hemiparesis) | Body | Scandinavian Stroke Scale |
| | | Brain | Mini Mental State Examination |
| Activity limitation | Function/observed behaviour (e.g. poor mobility) | Interaction of person and environment | modified Rankin Scale Barthel Index |
| Participation restriction | Social position/roles (e.g. unable to cook) | Person in their social context | Level of care |

In practice, the individual domains of impairment, activity limitation and participation restriction overlap substantially, especially after stroke. For example, motor and language dysfunction extensively affect all these domains simultaneously and therefore the clinical use of these sharp distinctions must be called in question.

In the following section, I will give an overview of different ways to describe outcomes after stroke and mention the specific scales that we have used in Paper I-III. I will give details about the specific scales later in the section on *Material and Methods*.

PATHOLOGY

In this thesis, I have defined clinical endpoints as a measure of pathology, like deaths or vascular events. Such ‘hard’ clinical endpoints are often chosen as the primary endpoint of a clinical trial. We have collected information about vascular events during long-term follow-up and used this data as endpoints in Paper III.

IMPAIRMENTS

The WHO-ICF defines *impairment* as problems in body function or structure as a significant deviation or loss (38). Measures of impairment is important for the evaluation of the stroke severity and is an obligatorily assessment in the emergency phase, according to the European Stroke Organisation (ESO)’s Guidelines for Management of Ischaemic Stroke 2008 (28). In general, impairment scales consist of several variables for observing the signs and symptoms of motor weakness, sensory and proprioceptive deficits and cognitive impairments at onset.

Impairment scales are frequently used in phase II trials and acute stroke studies, because they may be the most sensitive to change and have the greatest capacity to differentiate between treatment groups (39). Among these, common neurological impairment scales are the Scandinavian Stroke Scale (SSS) (40), which was chosen for the primary analysis in SCAST, and the National Institute of Health Stroke Scale (NIHSS) (41). Both scales are validated and share common measures of impairment, but differ in the weighting they give to individual items, the inclusion and exclusion of specific measures (e.g. SSS records hand strength and NIHSS commands) and in their direction of measurement (e.g. no impairment is 55/55 in the SSS and 0/42 in NIHSS) (42).

Around 60 % have some degree of cognitive impairment after stroke (43) and for dementia, the prevalence ranges from 6 – 32 %, depending on the diagnostic criteria and time of cognitive assessment (44). Cognitive function has not been systematically assessed as an outcome in acute stroke trials (45), despite the role as a predictor of long-term functional outcome (46). Cognitive impairment may negatively affect the rehabilitation process (47), making the evaluation of cognition especially interesting in patients who appear independent after stroke (modified Rankin Scale ≤ 2). Cognitive assessment is also important in patients who are dependent after stroke, despite minimal physical disability, to explain reasons for dependency and furthermore in patients with severe physical disability, since quality of life then depends on cognition (48).

Executive function, speed and attention, verbal memory, visual memory, perceptual skills and nominal skills are all domains that can be affected in varying levels, depending on location and size of stroke (49) and should be covered by assessment. We have used the Mini Mental State Examination (MMSE) as outcome measure for cognition (50). MMSE was originally developed to screen for dementia, but is widely used in stroke trials. It is fairly sensitive to

memory and language disorders and less sensitive to executive functioning and slight cognitive change (51;52). The Montreal Cognitive Assessment (MoCA) is a newer instrument, designed to be sensitive to mild cognitive impairment and to disturbances in executive functions (53;54), but has not been used in this thesis.

ACTIVITY LIMITATION

The WHO-ICF defines *activity limitations* (former disability) as difficulties in executing activities (38). Measures of activity are the most frequently used primary outcome in stroke trials and usually preferred for phase III trials. Among these, the modified Rankin Scale (mRS) (55) is the most common measure and was chosen for the primary effect variables in SCAST, followed by the Barthel Index (BI) (56). The modified Rankin Scale is a clinician-reported measure of global disability and the need for assistance. The broad categories subsume instrumental activities of daily living (e.g. meal preparation and shopping) and basic activities of daily living (e.g. walking, dressing and grooming) with a focus on motor function (57). It allows the clinician to consider cognition and social functioning, which may contribute to perceived disability (58) and distinguishes the modified Rankin Scale from basic activities of daily living-specific measures, such as the Barthel Index. The Barthel Index has a focus on self-care and mobility (59) and was used as endpoint in Paper II. It was originally developed as a scale used for rehabilitation, but is validated for stroke patients (60). Both scales demonstrate a strong correlation with measures of stroke pathology, such as infarct volumes, neurological impairment and other stroke scales (61;62).

PARTICIPATION RESTRICTION

The development of measures capturing the essence of participation has just begun, after the WHO introduced the term in the 1990s. The WHO-ICF defines *participation restrictions* (former handicap) as problems an individual may experience in involvement in life situations (38). It is relatively complex and more dependent on environmental influences and social support than the other domains of functioning. In my thesis, I have defined level of care required after stroke as a measure of participation (Paper II). In a review from 2007, both the modified Rankin Scale and the Barthel Index seemed to be predictors for level of care, even across countries and healthcare settings (63). This is important for patients, caregivers and the society. There are few clinical stroke trials assessing level of care and there is also a need for development of quantitative prognostic models for the modified Rankin Scale and the Barthel Index to improve individual predictions of recovery as a tool to aid clinical management (63).

HEALTH-RELATED QUALITY OF LIFE

Although not a part of the objective WHO-ICF, another useful concept of functioning is the patient-reported health-related quality of life, which we used in Paper I. The WHO defines *health* as a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity (64). Furthermore, the WHO defines *Quality of Life* as individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns (65). There is no universal definition of *health-related quality of life*, but from a medical point of view, the term may refer to those aspects of quality of life affected by disease. It is

multidimensional, comprising the four broad domains physical, functional, mental and social health (66). The objective aspects of health-related quality of life cover the patient's physical function, whereas the subjective aspects cover the feelings and perceptions and how the patients feel about their health status.

Until recently, few clinical stroke trials have assessed health-related quality of life, despite the association between cognitive impairment, functional outcome and health-related quality of life (67;68). It is now regarded as an important outcome in stroke trials (48), seen in light of the increase in stroke survival and the ageing of the population.

Health-related quality of life can be measured with generic or disease-specific measures. Generic measures are designed to compare health-related quality of life across populations or different diseases, whereas disease-specific measures are designed to assess health-related quality of life with questions and scales specific to a disease or condition. Commonly used quality of life-scales in stroke trials are the Stroke-Specific Quality of Life scale (SS-QoL) (69) and the two generic scales EuroQoL and the Short Form 36 (SF-36), which both appears to be valid in stroke patients (70;71). In this thesis, I have used the EuroQoL as a measure of health-related quality of life.

AIMS OF THE THESIS

The aim of the thesis was to assess the effect of blood pressure lowering treatment with candesartan in patients with acute stroke and elevated blood pressure on a variety of clinical outcomes and at two different intervals after stroke (6 months and 3 years).

The specific aims of the three individual studies were to study the effect of candesartan on

1. Cognitive function and quality of life at 6 months (Paper I);
2. Activities of daily living and level of care at 6 months (Paper II); and
3. Vascular events during 3 years' follow-up (Paper III).

MATERIAL AND METHODS

The primary aim of SCAST was to assess the effect of blood pressure lowering treatment with candesartan in patients with acute stroke and elevated blood pressure on functional outcome and the risk of vascular events during a 6 months' follow-up period. The analyses in this thesis are all pre-specified, secondary analyses of SCAST (72).

STUDY POPULATION

SCAST was a multicentre, randomised, placebo-controlled and double-blind trial of the angiotensin receptor blocker candesartan in patients with acute stroke and elevated blood pressure. Between June 2005 and February 2010, 2,029 patients were enrolled in nine North-European countries. Patients aged 18 years or older, with a clinical diagnosis of ischaemic or haemorrhagic stroke, presenting within 30 hours of symptom onset and with systolic blood pressure ≥ 140 mmHg were eligible for inclusion. Exclusion criteria were contraindications to or ongoing treatment with an angiotensin receptor blocker, markedly reduced consciousness (Scandinavian Stroke Scale score ≤ 2), clear indication, in the clinician's view, for an angiotensin receptor blocker during the treatment period (for example patients with chronic heart failure and intolerance to angiotensin converting enzyme inhibitors), clear indication for antihypertensive therapy during the acute phase of stroke, known pre-morbid modified Rankin Scale score ≥ 4 , life expectancy ≤ 12 months, patients unavailable for follow-up and pregnancy or breast-feeding (72).

STUDY TREATMENT AND FOLLOW-UP

Patients were randomly allocated to treatment with candesartan or placebo for 7 days, doses increasing according to a fixed-dose escalation scheme from 4 to 16 mg once daily during the first 3 days. In case of severe and sustained hypertension, additional antihypertensive drugs could be administered at the local investigators' discretion. In the follow-up period, candesartan was the advised antihypertensive treatment and was provided free of charge, but also this was at discretion of the local investigators. Clinical visits took place on day 7 and at 1 and 6 months (72).

Outcome assessment at 6 months was blinded by local investigators. The effect variables impairment (MMSE), activity limitation (Barthel Index) and health-related quality of life (EuroQol) were assessed by standardised interviews, whereas participation restriction (level of care) was derived from the place of residence.

Long-term follow-up was performed only in the Scandinavian countries (Norway, Sweden and Denmark), in accordance to the protocol. The patients' personal identification numbers were linked with the national patient registries and the cause of death registries (73-78). We extracted data for up till 3 years after randomisation, or until death, whichever came first. In Norway, data linkage with the Norwegian Patient Register was only possible from 2008 onwards, so for Norwegian patients included before 2008, we used data from the Cardiovascular Disease in Norway (CVDNOR) project (79). CVDNOR is a hospital-based register in Norway for the time period 1994 - 2009, originating from a research project conducted as collaboration between the University of Bergen and the Norwegian Knowledge Centre for the Health Services.

The national patient registries contain information about patients' contact with all public and private hospitals (inpatient and outpatient). For each hospitalisation, the registries include information about the date of admission and discharge, the primary diagnosis and a set of secondary diagnoses. We decided to only use inpatient data for the analysis, since CVDNOR only contained inpatient data. The cause of death registries include information about the date and cause of death.

EFFECT VARIABLES

VASCULAR EVENTS

We used the 10th version of the International Classification of Diseases (ICD-10) to define the endpoints in Paper III.

Stroke: Hospitalisation after the first 28 days of randomisation with a diagnosis of I61 (intracerebral haemorrhage), I63 (cerebral infarction) (except I63.6 [cerebral infarction due to cerebral venous thrombosis]), I64 (stroke, not specified as haemorrhage or infarction) or G45 (transient cerebral ischaemic attack).

Myocardial infarction: Hospitalisation with a diagnosis of I21 (acute myocardial infarction) or I22 (subsequent myocardial infarction), occurring any time after randomisation.

Vascular death: If death occurred within 28 days of onset of stroke or myocardial infarction, or if the cause of death was (G45) or R96 (other sudden death, cause unknown) or any diagnosis from chapter I (diseases of the circulatory system).

Death of all causes: All other causes of death.

MINI MENTAL STATE EXAMINATION

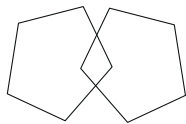
We assessed cognitive function by the Mini Mental State Examination (MMSE) (Paper I), a test which comprises 20 items providing information about orientation, registration, attention and calculation, delayed recall, language and construction. The MMSE has a maximum score of 30 points, where higher scores indicate better cognition (50). No optimum MMSE cut-off value has been identified (80) but based on the left-skewed distribution of the MMSE scores, we decided to trichotomise MMSE into ‘definite’ (≤ 23 points), ‘possible’ (24 - 27) or ‘no cognitive impairment’ (≥ 28 points) (50;81). We included all patients with less than two missing components of the MMSE in the analysis and assigned missing components the score 0 (maximum deficit).

Figure 1: Mini Mental State Examination (50)

| | | Maximal score |
|--|---|------------------|
| Orientation | Name of year? Season? Month? Date? Day of the week? | 5 |
| | Name of the country? District? Town? Hospital? Ward? | 5 |
| Registration | Name three objects. Repeat until patient learns all three. Ask patients to repeat all three. | 3 |
| Attention and calculation | Spell a word backwards (the investigator chooses a word of four to five letters), or subtract 7 from 100, then repeat from results. Repeat five times (answers: 100, 93, 86, 79, 72, 65). | 5 |
| Recall | Ask for the three objects chosen earlier. | 3 |
| Language | Show a pencil and a watch and ask patient to name them. | 2 |
| | Repeat a period (the investigator chooses a period of four to five words). | 1 |
| | A three-stage command: <i>Take this piece of paper in your right hand, fold it in half and put it on the floor.</i> | 3 |
| | Point below to "Close your eyes" (written in patient's language) and ask patient to obey what is written. | 1 |
| | Ask the patient to write a sentence below (score 1 point if the sentence is sensible and has a verb and a subject). | 1 |
| | Ask the patient to copy the diagram below | 1 |

Write "Close your eyes" in the patient's language

Sentence: _____



BARTHEL INDEX

We measured activities of daily living with the Barthel Index (Paper II), a 10-domain scale measuring activities related to self-care (feeding, bathing, grooming, dressing, bowel care, bladder care and toilet use) and mobility (transfers, mobility and stair climbing) (59). The Barthel Index is determined by observation of patients in a number of tasks, although items regarding bowel and bladder continence are obtained by history. The values assigned to each of the 10 domains are based on time and amount of physical assistance required for a patient unable to perform a common daily activity. We used 5-point-increments, which gives a maximal score of 100 points (independent), and presented the scale as a total score, as well as each domain individually. There are no optimal definition of a ‘good’ Barthel Index outcome (82). We decided to divide the total score into three categories: ‘dependency’ (≤ 55 points), ‘assisted independency’ (60 - 90), or ‘independency’ (≥ 95), based on the distribution of the Barthel Index scores and previous used cut-off scores (82;83). Barthel Index scores were not calculated if any of the 10 domains was missing.

Figure 2: Barthel Index (59)

| | |
|--------------------------------------|---|
| | Score |
| Feeding | 0 = unable 5 = needs help cutting, spreading butter, etc, or requires modified diet 10 = independent |
| Bathing | 0 = dependent 5 = independent (or in shower) |
| Grooming/personal care | 0 = needs to help with personal care 5 = independent face/hair/teeth/shaving (implements provided) |
| Dressing | 0 = dependent 5 = needs help but can do about half unaided 10 = independent (including buttons, zips, laces, etc) |
| Bowels | 0 = incontinent (or needs to be given enemas) 5 = occasional accident 10 = continent |
| Bladder | 0 = incontinent, or catheterised and unable to manage alone 5 = occasional accident 10 = continent |
| Toilet use | 0 = dependent 5 = needs some help, but can do something alone 10 = independent (on and off, dressing, wiping) |
| Transfers (bed – chair – bed) | 0 = unable, no sitting balance 5 = major help (one or two people, physical), can sit 10 = minor help (verbal or physical) 15 = independent |
| Mobility (on level surfaces) | 0 = immobile or <50 m 5 = wheelchair independent, including corners, >50 m 10 = walks with help of one person (verbal or physical) >50 m 15 = independent (but may use any aid; for example stick) >50 m |
| Stairs | 0 = unable 5 = needs help (verbal, physical, carrying aid) 10 = independent |

LEVEL OF CARE

Level of care can be considered as an indirect measure of participation and was used in Paper II. In our analysis, the outcome is derived from the variable ‘place of residence at 6 months’, with the answer options ‘own home (or with family/friend), without public help (home-based nursing, etc)’, ‘own home (or with family/friend), with public help’, ‘institution for rehabilitation’, or ‘institution for long/permanent stay (nursing home, etc)’. By adding the two intermediate categories, we ended up with a trichotomisation of level of care. Missing responses were not replaced.

EURO-QOL

The EuroQoL-instrument assesses health-related quality of life in two parts, a descriptive system and a visual analogue scale (84;85) (Paper I). The first part comprises five domains (EQ-5D; mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and each domain is scored on a three-point ordinal scale (no problems, some problems, severe problems). We presented these domains individually, but also combined into an overall index (EQ-5D index) which takes into account the response pattern in all five domains: A unique health state is defined by combining one level of perceived problems from each of the five domains, which gives a total of 243 possible health states. By using the Time-Trade-Off method and an algorithm that has previously been validated in a representative sample of UK patients, the unique health states were given a score ranging from +1.00 (for health state 11111, defined by EuroQoL as ‘perfect health’) to -0.59 (for health state 33333, defined by EuroQoL as ‘worse than death’) (86;87). The second part of the EQ-5D consists of a visual

analogue scale (EQ-VAS), where patients are asked to rate their perception of their overall health with ‘best imaginable health state’ set at 100 and ‘worst imaginable health state’ set at 0. Only patients with complete data for EQ-5D or EQ-VAS were included in the analysis.

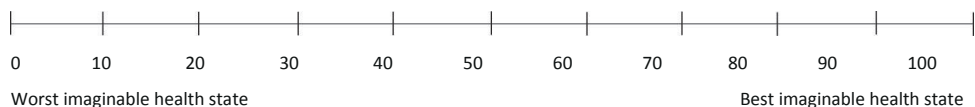
Figure 3: EuroQoL (84)

Please ask the patient

1) *Please indicate which statements best describe your health state today*

| | |
|--|---|
| Waking about | No problems / Some problems / Confined to bed |
| Self-care (e.g. washing, dressing) | No problems / Some problems / Unable |
| Usual activities (work/study, family/leisure) | No problems / Some problems / Unable |
| Pain or discomfort | None / Moderate / Extreme |
| Anxiety or depression | None / Moderate / Extreme |

2) *We have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked by 100 and the worst state you can imagine is marked by 0. How good or bad is your current health state? Please indicate by setting a mark on the scale.*



STATISTICAL ANALYSES

All analyses were pre-specified as secondary analyses in the SCAST protocol. The original Statistical Analysis Plan specified that an ordinal method should be used for the primary analysis. As the method leads to a substantial increase in statistical power, ordinal regression was also the preferred statistical method for the secondary analyses. We trichotomised the assessment scores and calculated odds ratio with ordinal logistic regression after controlling that the assumptions of proportional odds were not violated (Paper I and Paper II). Multiple linear regression was used otherwise (Paper I). Cox proportional hazards regression model was used for the analysis of all long-term endpoints (Paper III). All analyses were adjusted for the pre-defined prognostic variables age, type of stroke (ischaemic vs. all other), systolic blood pressure and Scandinavian Stroke Scale score at baseline. Pre-specified subgroup analyses were performed for all effect variables (except recurrent stroke and all-cause death [Paper III]) and the p-values represent the interaction between each subgroup and trial treatment. We used SPSS Statistics version 18.0 and 20.0 for all analyses.

ETHICS

Written informed consent was sought from all patients and non-written or waiver of consent was accepted only after approval from the ethics committees. The linkage of data from the SCAST database to the national patient registries, the cause of death registries and CVDNOR were approved by the Regional Ethics Committee and The Norwegian Data Protection Authority. The trial complied with Good Clinical Practice standards and with the Declaration of Helsinki (88).

SUMMARY OF RESULTS

Of the 2,029 patients included in the trial, 1,876 were alive at 6 months. Demographic and clinical characteristics were well balanced between treatment groups, except that there were fewer women (39 versus 43%) and more patients with a history of stroke or TIA (24 versus 20%) in the candesartan group. The mean age was 70 years, mean symptom duration before randomisation was 18 hours, mean Scandinavian Stroke Scale score was 42 and mean blood pressure was 171/90 mmHg. 86% of the patients had a diagnosis of ischaemic stroke and 13% had haemorrhagic stroke. During the 7 days treatment period blood pressure was significantly lower in patients allocated candesartan ($p < 0.001$) and the mean difference in blood pressure on day seven was 5/2 mmHg.

PAPER I

The purpose of this study was to investigate the effect of candesartan in patients with acute stroke and elevated blood pressure on cognitive function and health-related quality of life at 6 months.

We analysed data on MMSE scores, EQ-5D indices and EQ-VAS scores in 1,644 (81%), 1,734 (85%) and 1,697 (84%) patients, respectively. The patients with missing data suffered from more severe stroke. For all three outcome scales, data completeness was similar in the candesartan group and placebo group.

The patients had a high cognitive function with a median MMSE score on 28/30 in both groups, and we did not find any significant difference between the distributions of MMSE scores in the two groups.

The patients treated with candesartan had a lower score on both parts of the EuroQoL compared to patients given placebo, and for the EQ-5D index, the difference was small, but statistically significant ($p = 0.034$). For the individual EQ-5D domains there were also small differences in disfavour of candesartan.

There was no evidence of a differential effect of candesartan in any of the pre-specified subgroups, or among patients with or without recurrent stroke in the follow-up.

PAPER II

In the second paper, we investigated the effect of candesartan in patients with acute stroke and elevated blood pressure on activities of daily living and level of care at 6 months.

Data on the Barthel Index and level of care were available in 1,780 (88%) and 1,825 patients (90%), respectively. As in Paper I, the patients with missing data were older and suffered from more severe stroke, but for both outcome scales, data completeness was similar in the candesartan group and placebo group

The patients in both treatment groups had overall high Barthel Index scores and 75% in both groups lived at home with no public help. We did not find any treatment effect of candesartan for neither the Barthel Index nor level of care. We accounted for national differences in the analyses of level of care and again found no beneficial effects of candesartan.

We also assessed the effect of candesartan on the 10 individual Barthel Index domains, and there was again no treatment effect of candesartan in the domains. However, for mobility the difference was nearly significant.

For the subgroup of patients with a lacunar stroke, there was a difference in disfavour of candesartan, but only for the Barthel Index (p for interaction = 0.02). For the subgroups of patients with or without a history of hypertension, there was also a significant difference in treatment effect, but only for level of care (p for interaction = 0.03).

PAPER III

The aim of the third paper was to see whether blood pressure lowering treatment with candesartan in the acute phase of stroke could lead to benefits that became apparent over a period of 3 years.

Long-term data were available from 1,256 patients of all 1,286 Scandinavian patients in the trial (98%). Data completeness was similar in the candesartan group and placebo group. For the last 96 patients included in the trial, we did not have follow-up data for the full period of 3 years, because of delays in the updating of the registries. The median follow-up time for these patients was 2 years and 4.5 months, and they were evenly distributed between the candesartan group and the placebo group.

The risk of the primary composite endpoint of stroke, myocardial infarction or vascular death during 3 years' follow-up did not differ significantly between the candesartan and placebo group (adjusted hazard ratio [HR] 0.87, 95% confidence interval [CI] 0.71–1.07, $p = 0.19$).

There were also no statistically significant differences for the secondary endpoints stroke and all-cause death, nor in any of the pre-specified subgroups.

DISCUSSION

INTERPRETATION OF RESULTS

Our analyses of secondary effect variables in SCAST showed no beneficial effect of blood pressure lowering treatment with the angiotensin receptor blocker candesartan in patients with acute stroke and elevated blood pressure.

The results were consistent for short- and long-term follow-up, across different types of effect variables and with studies suggesting an association between cognitive impairment, activity limitation and health-related quality of life (67;68) and between cognitive impairment, activity limitation and level of care (63).

Our results are consistent with a meta-analysis of previous trials of several strategies to lower blood pressure (34), and with the recent China Antihypertensive Trial in Acute Ischemic Stroke (CATIS) (89) and the Efficacy of Nitric Oxide in Stroke (ENOS) trial (90). The CATIS trial randomised 4,071 patients with acute ischaemic stroke within 24 hours to an antihypertensive treatment intervention or to discontinuation of antihypertensive. The study showed no effect on death or major disability at 14 days or hospital discharge. The ENOS trial assessed whether blood pressure could be safely lowered with a daily glyceryl nitrate patch for 7 days after acute stroke, and whether antihypertensive drugs should be continued or withdrawn. 4,011 patients with acute ischaemic or haemorrhagic stroke were enrolled within 48 hours, and functional outcome at day 90 did not differ in either treatment comparison.

An update of the Cochrane review on vasoactive drugs found no overall beneficial effects on death or dependency, nor in subgroups according to drug class, stroke type or time to treatment (91). We did not identify any trial with long-term follow-up (more than 12 months).

Next, I will discuss the findings derived from each of the three studies. Furthermore, I will discuss strengths and limitations of our analyses, the implications of our findings and suggest directions for future research.

EFFECTS OF CANDESARTAN IN ACUTE STROKE ON COGNITIVE FUNCTION

Long-term treatment with inhibitors of the renin-angiotensin system has been shown to reduce the risk of cognitive impairment after stroke (92;93). We found no such effects from treatment with the angiotensin receptor blocker candesartan in the acute phase of stroke.

There are many possible explanations for the discrepancy between our results and the results of secondary prevention trials. First, the treatment period in our trial may have been too short for candesartan to have any protective effect on cognitive function. The duration of the antihypertensive treatment seems to be associated with a reduced risk for dementia and cognitive decline, as seen in a trial of 848 patients (94). Second, the patients in SCAST had a high cognitive level, which may have hidden small differences between the candesartan and placebo groups because of the ceiling effect (51). Additionally, the MMSE is not a scale measuring one particular cognitive concept, but an aggregation of 11 very different clusters. Because of this, two identical MMSE scores may hide different patterns of cognitive impairment. Previous studies of the MMSE has yielded conflicting results regarding optimal cut-offs and sensitivity for detection of cognitive impairment after stroke (52;80;95). In this

context, a third explanation for the neutral result on cognition could be that patients in the two groups had different types of neurological deficits, for example different degrees of hand paresis and dysphasia, which can influence the MMSE scores and mask differences in other cognitive functions (96). However, the distribution of neurological deficits including hand paralysis and aphasia was identical for both groups, which rules out the possibility that misclassification of cognitive function can explain the neutral result. Finally, the neutral result of candesartan on the risk of recurrent stroke at 6 months (34) may also explain the neutral result for cognition. If the benefits of treatment is a result of prevention of stroke, as suggested by The Perindopril Protection Against Recurrent Stroke Study (PROGRESS (93), it is no surprise that candesartan had no effect on cognitive function in our trial.

EFFECTS OF CANDESARTAN IN ACUTE STROKE ON ACTIVITIES OF DAILY LIVING

We examined the effect of candesartan in acute stroke on activities of daily living at 6 months, but found no beneficial effects. Rather, there were weak signals of harmful effects of candesartan. This is consistent with the result of the primary analysis of modified Rankin Scale (34) and with previous findings suggesting a high correlation between the modified Rankin Scale and the Barthel Index (97). Similarly, in the recent ENOS trial, patients assigned to continue their antihypertensive drugs did worse than those who stopped taking drugs for activities of daily living (90).

The overall high Barthel Index score in SCAST may have hidden small differences in treatment effect. Many important activities are not included in the Barthel Index, such as cooking, grocery shopping and outdoor walking. Even though these items are explicitly excluded from the Barthel Index, each of them could have a substantial effect on

independence. Thus, the scale suffers from a ceiling effect, wherein the maximum score can be achieved even in many disabled patients, making it difficult to detect an intervention effect on activities of daily living (98;99). The modified Rankin Scale is found to be a better instrument in differentiating between changes in mild to moderate activity limitation (99). However, both the modified Rankin Scale and the Barthel Index have shown good clinimetric properties for measuring disability in stroke patients (62;100).

Candesartan was associated with a higher risk of harm in the subgroup of patients with lacunar stroke. This was only found for activities of daily living and may well be a chance finding, but one can also speculate whether patients with lacunar strokes are more sensitive to blood pressure lowering treatment, because of the rightward shift of the auto-regulatory curve in patients with high blood pressure (27;101). In another secondary analysis of SCAST, a similar indicative result was identified in patients with different types of ischaemic stroke (102).

EFFECTS OF CANDESARTAN IN ACUTE STROKE ON LEVEL OF CARE

We found no beneficial effects of candesartan given in the acute phase of stroke on level of care at 6 months. Again, there were weak signs of a negative effect of candesartan. This is consistent with our results of activity limitation, measured by the modified Rankin Scale and the Barthel Index, which both are found to be predictors for level of care (63). Furthermore, it is consistent with our result of cognitive impairment, which together with stroke severity and dependence in activity of daily living, seems to be associated with health care resources and costs, as suggested by The Göteborg 70+ Stroke Study (103). Until now, the second Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT2) has been the

only acute stroke trial that assessed level of care. 2,794 patients with primary intracerebral haemorrhage were randomised to intensive blood pressure lowering (target systolic level < 140 mmHg within 1 hour) or guideline based treatment (target systolic level < 180 mmHg) within 6 hours of symptom onset, and no beneficial effect of intensive blood pressure lowering was observed on the effect variable level of care (104).

Level of care is a crude outcome measure and depends on a number of cultural and social factors, such as family situation and availability of public care. We accounted for national differences in the analyses and again found trends disfavouring candesartan. In addition to being an indicator of participation, level of care is an indicator of long-term costs of treatment and adds information about effects of treatment that is not conveyed by the Mini Mental State Examination, modified Rankin Scale and the Barthel Index (105).

EFFECTS OF CANDESARTAN IN ACUTE STROKE ON HEALTH-RELATED QUALITY OF LIFE

We measured health-related quality of life at 6 months after short-term treatment with candesartan, but did not find any beneficial effect. Rather, there were signs of a negative effect of candesartan. This could either suggest that treatment with candesartan in the acute phase may actually be detrimental, or more likely that the result is neutral, based on the small differences in the EQ-5D index (106). The latter is consistent with the ENOS trial, where there was no effect on the EQ-VAS with either glyceryl trinitrate or of continuing prestroke antihypertensive drugs (90).

Blood pressure lowering treatment with candesartan may be associated with positive effects on health-related quality of life in elderly patients without previous stroke (107).

INTERACT2 indicated that haemorrhagic stroke patients treated with intensive blood pressure lowering within 6 hours had significantly better health-related quality of life (assessed by the EQ-5D index) at 90 days than those in the standard-therapy group (104). We assessed the effect of candesartan for these subgroups in SCAST, but could not find any differences, whether in the subgroup of patients with haemorrhagic stroke or in the patients treated very early (within 6 hours).

On a general level, one might ask whether EuroQol is a good measure of ‘health-related quality of life’, or whether it is simply a measure of ‘patient-reported outcomes’ (108). However, for this analysis we have chosen to apply the EuroQoL instrument in a traditional manner (84).

EFFECTS OF CANDESARTAN IN ACUTE STROKE ON VASCULAR EVENTS DURING LONG-TERM FOLLOW-UP

Paper III represents the long-term effects of blood pressure lowering treatment in acute stroke. In this analysis, we examined the long-term effects of candesartan on the primary endpoint vascular events and the secondary endpoints recurrent stroke and all-cause death, but could not find any beneficial effects of candesartan.

For recurrent stroke, we observed a small difference in favour of candesartan, similar to what was observed in the ACCESS study (32) and in trials of angiotensin-receptor blockers for secondary prevention (109;110). However, the differences for both the cumulative risk of stroke and for the severity of recurrent stroke were statistically non-significant and there was no effect on all-cause death.

There are certain issues with the use of registry based information. First, details regarding the severity of the disease, medication use, blood pressure, and other clinical information are missing. Second, patients with less severe forms of stroke are not always hospitalised, and the estimates based on our registry data will underestimate the true occurrence of recurrence. However, the randomisation of a large number of patients will probably have ensured an equal distribution of these factors between treatment groups. Third, the diagnostic accuracy of the ICD-10 diagnostic codes relies on the quality of coding of a large number of physicians. As a sensitivity analysis, we performed an analysis of endpoints up to 6 months using data from the national patient registries, and compared this with the analysis of data from the 6 months' visit in the trial, and found virtually identical results.

STRENGTHS AND LIMITATIONS

Randomised controlled trials are the most reliable methods of determining the effects of treatment. Design and conduct must minimise the possibility of bias (internal validity) but to be clinically useful the results must also be relevant to a definable group of patients in a particular clinical setting (external validity). I believe SCAST meets these criteria.

The main strengths of SCAST are the randomisation of a large number of patients and the low risk of observation bias, due to masking of study treatment and blinded collection of data. The random allocation of treatment assured well balanced demographic and clinical characteristics between treatment groups. All analyses were adjusted for pre-defined key variables. These procedures have ensured the internal validity. I also believe the study has high external validity. First, the patients are included from multiple centres (both local and university hospitals) in nine countries and constitute a representative sample of stroke patients admitted

to stroke services in the western world. Second, the inclusion criteria were broad, including both patients with ischaemic and haemorrhagic stroke and with systolic blood pressure ≥ 140 mmHg. Patients were excluded for reasons that are common in clinical practice, most frequent were symptom duration > 30 hours and systolic blood pressure < 140 mmHg (34). Third, we assessed a variety of clinical outcomes, both clinical- and patient reported, at 6 month. Due to linkage with nation-wide, automatically updated patient registries in the Scandinavian countries, we were also able to perform a long-term follow-up after randomisation of nearly all Scandinavian patients included in the study (Paper III).

Another strength of our analyses is the use of ordinal regression for the analysis of outcome. Conventionally, stroke trials use binary outcome events, for example ‘stroke’ versus ‘no stroke’, or dichotomise ordinal outcome scales, for example MMSE into ‘cognitive impairment’ versus ‘no cognitive impairment’. Clinical relevant data, such as the severity of an event, may get lost using a binary approach. An ordinal approach will account for the differences in severity using ordered categorical data within vascular outcome events or outcome scales, leading to more efficient and reliable results (111;112). However, it assumes that treatment effect is similar across outcome levels (‘proportionality of odds’), meaning that the underlying odds ratios are virtually the same for each step on the MMSE.

The original Statistical Analysis Plan also specified that the time to first event of the composite vascular endpoint should be analysed by the Cox proportional hazards regression model (Paper III). This analysis assumes that the risk of event within the two groups remains constant over time. Due to possible violation of the proportional hazards assumption, we performed a sensitivity analysis using logistic regression and found virtually identical results.

The main limitation was that the trial was powered for the primary outcomes functional outcome and vascular events at 6 months and not for the secondary outcomes. Additionally,

the patient recruitment was stopped earlier than planned and did not reach the original target of 2,500 patients (34). However, for cognitive function and health-related quality of life (Paper I) and activities of daily living and level of care (Paper II), the results were consistent with the result of the primary analysis. For the long-term follow-up, data linkage was only possible for the Scandinavian patients and the analysis includes only two-thirds of the patients included in SCAST. In this case, our analysis lacks sufficient power to be able to draw firm conclusions.

CONCLUSION AND FUTURE DIRECTIONS

We found no evidence of a beneficial effect of blood pressure lowering treatment with an angiotensin receptor blocker in patients with acute stroke and elevated blood pressure. The result is consistent with the results of the primary analysis, and support the conclusion in the main report that there is no indication for routine blood pressure lowering treatment with candesartan in the acute phase of stroke (34).

Despite the results of several trials the past 3 years, the debate regarding blood pressure lowering continues and several questions remain.

Should we differentiate treatment according to stroke subtype?

INTERACT2 indicated that lowering of blood pressure might be efficacious only in patients with haemorrhagic stroke, and have led to changes in the European Stroke Organisation guidelines (113). A recent population-based study of 636 patients with acute stroke compared all acute stroke blood pressure readings with premorbid readings. The findings suggest that high post-stroke blood pressure might be due to an increase in the hours or days before the event, especially in patients with intracerebral haemorrhage. This might be an explanation for why the risks and benefits of lowering blood pressure acutely after stroke might be expected to differ (114). The Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) II is designed to look into the effectiveness and safety of using intravenous Nicardipine within 3 hours of onset of intracerebral haemorrhage (115). The trial has recruited nearly 60% of an estimated 1,280 patients and results are expected in 2016. Furthermore, the Blood pressure in

Acute Stroke Collaboration plans an individual patient metanalysis of blood pressure lowering in intracerebral haemorrhage. Both will hopefully contribute to a stronger level of evidence.

Another unanswered question is whether blood pressure should be lowered in patients with ischaemic stroke eligible for thrombolysis. This question will hopefully be answered in the Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED), which aims to assess whether intensive blood pressure lowering (130-140 mmHg target) improves outcomes compared with the guideline-recommended level (systolic blood pressure ≤ 185 mmHg) in patients eligible for thrombolysis in acute ischaemic stroke (116).

Is time of importance?

Blood pressure peaks in the first minutes after stroke onset (114), at which point any adverse pathophysiological effects might make the most impact. ENOS and INTERACT2 have both suggested potential benefits of blood pressure lowering when initiated within 6 hours (90;104).

The pilot trial Rapid Intervention With Glyceryl Trinitrate in Hypertensive Stroke (RIGHT) showed that ultra-acute blood pressure lowering (< 4 hours) with glyceryl trinitrate in 41 patients with probably stroke was safe (117). The planned RIGHT-2 will further examine the difference between glyceryl trinitrate and no glyceryl trinitrate in suspected ultra-acute stroke, as well as the feasibility of an ambulance-based trial (118). Similarly, the ongoing Field Administration of Stroke Therapy-Blood Pressure Lowering (FAST-BP) is an open, dose-escalation study of glyceryl trinitrate, evaluating the feasibility, safety and physiologic efficacy of field-initiated glyceryl trinitrate in 45 patients within 2 hours of suspected stroke (119).

This thesis illustrates that future acute stroke trials of blood pressure lowering should include outcomes on cognitive status and health-related quality of life as a complement to functional outcome and also consider the effects of long-term outcomes.

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ERRATA

| Page | Line | Original | Correction |
|------|---------|---|---|
| 3 | 5-6 | <u>INTRODUCTION...</u> <u>HIGH BLOOD (...)</u> | <u>INTRODUCTION...</u> <u>HIGH BLOOD (...)</u> |
| 10 | 5-6 | <i>Stroke 2013 (...)</i> II: Effects of (...) | <i>Stroke 2013 (...)</i> II: Effects of (...) |
| 31 | 5 | Figure 3: EuroQoL (84) | Figure 3: EuroQoL (84) |
| 43 | 10 | (...) identical results | (...) identical results. |
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| 52 | Ref. 64 | CONSTITUTION of the (...) | Constitution of the (...) |

